IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELI LILLY AND COMPANY and THE TRUSTEES OF PRINCETON UNIVERSITY, Plaintiffs, v. TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, and BARR LABORATORIES, INC., Defendants.	)	C.A. No. 08-335-GMS

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Eli Lilly and Company and the Trustees of Princeton University (collectively, "the plaintiffs") allege that defendants Teva Parenteral Medicines, Inc., APP Pharmaceuticals, LLC and Barr Laboratories, Inc. (collectively, "the defendants") filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") to manufacture and sell a generic version of ALIMTA® prior to the expiration of U.S. Patent No. 5,344,932 ("the '932 patent"). (D.I. 1.) In response, the defendants contend that the '932 patent is invalid under the doctrine of obviousness-type double patenting because the claimed invention is an obvious modification of inventions claimed in commonly-owned U.S. Patent Nos. 5,028,608 ("the '608 patent") and 5,248,775 ("the '775 patent) in light of the relevant prior art. (D.I. 11.)

The court held a five-day bench trial in this matter from November 8, 2010 through November 15, 2010. (D.I. 107 - 111.) After the presentation of the evidence, the court ruled in favor of the plaintiffs, having determined that the credibility of the plaintiffs' witnesses substantially outweighed the evidence presented by the defendants. (D.I. 111 at 1114:10-13.) Presently before the court are the parties' proposed post-trial findings of fact and conclusions of law. (D.I. 102; D.I. 103.) Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that the '932 patent is not invalid for obviousness-type double patenting. Having ruled in favor of the plaintiffs at trial, the court adopts the majority of the plaintiffs' proposed findings of fact and conclusions of law.[1] The court addresses the defendants' arguments in response to the court's ruling below.

II. LEGAL STANDARD

The doctrine of obviousness-type double patenting prevents a patentee from extending the term of exclusivity for a single invention by obtaining additional patents with only slight variations from the original invention. *See Takeda Pharm. Co., Ltd. v. Doll*, 561 F.3d 1372, 1375 (Fed. Cir. 2009). Obviousness-type double patenting "prohibits claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." *Sun Pharm. Indus.,*

[1]In accordance with well-established Federal Circuit precedent, the court concludes that secondary considerations are not relevant to the analysis of invalidity for obviousness-type double patenting. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 n.1 (Fed. Cir. 2003) ("Obviousness requires inquiry into objective criteria suggesting non-obviousness; nonstatutory double patenting does not."). As a result, the court shall not adopt the plaintiffs' proposed findings of fact and conclusions of law to the extent that they pertain to secondary considerations. Specifically, the court rejects Section IV of the plaintiffs' proposed findings of fact and Section III of the plaintiffs' proposed conclusions of law. (D.I. 102.)

Ltd. v. Eli Lilly & Co., 611 F.3d 1381, 1384 (Fed. Cir. 2010) (internal quotations omitted). "The obviousness-type double patenting analysis entails two steps: (1) construction of the claims in the earlier patent and the claim in the later patent to identify any differences, and (2) determination of whether the differences in subject matter between the claims render the claims patentably distinct." *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009). The second step of the analysis is analogous to an obviousness analysis under 35 U.S.C. § 103 in that the court must determine whether a person of ordinary skill in the art would consider the later invention an obvious variation of the prior invention. Id. at 1361-62.

III. DISCUSSION

A. The '775 Patent

1. Specification

According to the defendants, the '932 patent is invalid in view of the specific and general utility disclosed for the '775 intermediate in the '775 patent specification. (D.I. 103 at ¶¶ 33-43.) Specifically, the defendants contend that examples 6 and 10 of the '775 patent specification disclose the utility of the '775 intermediate as it pertains to making pemetrexed, thereby barring the plaintiffs from claiming the utility of the '775 patent in the subsequent '932 patent under the obviousness-type double patenting analysis. (Id. at ¶¶ 33-35.) Even though the '775 patent claims multiple uses, the defendants contend that the obviousness-type double patenting analysis encompasses any use for the compound which is disclosed in the specification of the earlier patent. (Id. at ¶ 38.) The defendants further contend that the '775 patent discloses a general utility for the claimed compounds because the evidence at trial identified pemetrexed as the only

compound within the scope of Formula I[2] that a person of ordinary skill in the art would make from the '775 intermediate. (Id. at ¶¶ 40-42.)

The court concludes that the examples found in the '775 patent specification do not support a finding of invalidity for obviousness-type double patenting because this case does not present a situation in which separate patents are sought for a claim to a compound and a claim to using that compound for the disclosed utility of the original compound. Generally, the law of double patenting has involved only what is claimed in the patent itself,[3] and the specification

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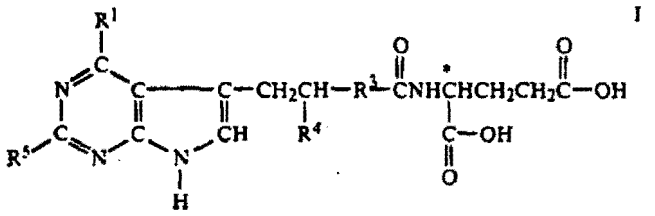
[2]Formula I of the '775 patent is disclosed as follows:



This formula discloses an antineoplastic glutamic acid derivative in which R^1 is — OH or — NH_2; R^3 is phenylene, thienediyl, furanediyl, cyclohexanediyl, or alkanediyl; R^4 is hydrogen, methyl, or hydroxymethyl; and R^5 is hydrogen, methyl, or amino. ('775 patent, col. 1:19-34.)

[3]The court acknowledges that the law is unsettled with respect to the role of the specification, as opposed to the claims, in the double patenting analysis:

> Until recently the law of double patenting was clear, but it has become distorted by divergent statements, leading to this flawed ruling. Until recently it was beyond dispute that the law of double patenting is concerned only with what is patented - that is, what is claimed. To determine whether there is double patenting it is the claims that are compared . . . The specifications of the patents are irrelevant to the double patenting analysis, other than to guide in construing the claims.

Sum Pharm. Indus., Ltd. v. Eli Lilly & Co., 625 F.3d 719, 721 (Fed. Cir. 2010) (Newman, J., dissenting) (contending that the law of double patenting is contrary to the panel's holding that claims to the anticancer use of a compound were invalid because the anticancer use was

serves as a guide in construing the claims. *See Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1277 (Fed. Cir. 1992) ("Double patenting is altogether a matter of what is claimed."). Recent Federal Circuit cases indicate that the specification is also relevant in situations in which the patentee claimed a compound in the first patent and later claimed a method of using the compound for the disclosed purpose, or claimed the same compound with an added limitation to a particular use in the subsequent patent. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1386 (Fed. Cir. 2003); *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008); *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010). Contrary to the defendants' contentions, however, the facts of the instant case can be distinguished from the facts set forth in *Geneva*, *Pfizer* and *Sun* because the '932 patent does not claim the use of the '775 compound, nor does it disclose a claim limitation directed to any compound claimed in the '775 patent. (D.I. 111 at 933-36.)

The court further concludes that the defendants impermissibly use examples 6 and 10 of the '775 patent specification as if the specification were a prior art teaching for purposes of the obviousness analysis. Federal Circuit precedent makes clear that the specification of the earlier patent cannot be used in a double patenting analysis as if it were a prior art teaching because this would constitute an improper use of hindsight knowledge of pemetrexed in determining whether pemetrexed would have been an obvious variant of the '775 compound. *In re Baird*, 348 F.2d 974, 979-80 (C.C.P.A. 1965). Thus, the defendants cannot look to the '775 patent for what it

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mentioned, but not claimed, in the continuation-in-part specification). Regardless, the limited circumstances in which the specification is relevant to the double patenting analysis under Federal Circuit precedent do not apply in this case. As previously discussed, the disputed claims of the '932 patent do not disclose a method of using the '775 compound.

would teach to a person of ordinary skill in the art. *Id.*

2. Person of ordinary skill in the art

The defendants next contend that even if the court does not rely on the '775 patent's specification in its analysis, the '932 patent is still invalid for obviousness-type double patenting because a person of ordinary skill in the art would immediately recognize the '775 compound as an intermediate that would be used to make pemetrexed. (D.I. 103 at ¶ 44.) The defendants cite expert testimony indicating that a person of ordinary skill in the art would expect to be able to convert the '775 intermediate to pemetrexed through the synthetic steps of hydrolysis and hydrogenation. (Id. at ¶ 45.) Moreover, the defendants contend that a person of ordinary skill in the art would not keep the triple-bond in the bridge of the final compound when every other active antifolate has a single bond in the bridge. (Id. at ¶¶ 46-47.)

The court concludes that pemetrexed would not have been an obvious variation of the '775 patent. The evidence presented at trial indicates that a person of ordinary skill in the art would have thought that the '775 compound was intended to be an intermediate for making a potential TS inhibitor[4] with a triple bond. (D.I. 111 at 962-77.) By leaving the triple bond unchanged, a person of ordinary skill in the art would not obtain pemetrexed as the resulting compound. (Id.) Moreover, the person of ordinary skill in the art would have no reason to make pemetrexed from among the many final antifolates suggested by the '775 compound because TS was generally the preferred antifolate target during the relevant time period. (D.I. 111 at 979-81.)

[4]Thymidylate synthase, or TS, is an enzyme in the folic acid pathway that has been considered as a potential target for antifolate cancer drugs. (D.I. 103 at ¶ 7.) TS inhibitors, unlike other antifolates, only make components of DNA, not RNA, and were therefore considered as less likely than other antifolates to have adverse effects on healthy cells. (Id. at ¶¶ 7-8.)

Instead, a person of ordinary skill in the art would make structural changes to the compound such as switching to a methyl group at the 2-position and using a carbon-nitrogen bridge or a carbon-carbon bridge with an ethyl portion, none of which would result in pemetrexed. (Id.) The changes a person of ordinary skill in the art might make to the '775 intermediate to achieve GARFT or DHFR inhibitors would likewise not lead to pemetrexed. (Id.) A person of ordinary skill in the art would not make the changes suggested by the defendants because those modifications would result in a TS inhibitor with an undesirable 2-amino, phenyl combination that was known to cause toxicity problems in in vivo studies. (Id. at 984:15-18.)

B. The '608 Patent

With respect to the '608 patent, the defendants contend that a person of ordinary skill in the art would change the thienyl in the '608 patent to a phenyl, resulting in pemetrexed. (D.I. 103 at ¶ 53.) In support of this contention, the defendants note that all promising antifolates during the relevant time period had a phenyl in the aryl position. (Id. at ¶¶ 54-55.) According to the defendants, a person of ordinary skill in the art engaged in the development of antifolates would have made small changes to a portion of an existing molecule to create a new molecule, and would have then made predictions regarding the biological activities of the resulting compound. (Id. at ¶¶ 51-52.) The defendants further contend that a person of ordinary skill in the art would rely on the principles of biosiosterism, a common technique employed in the rational design of new drugs, to change the thienyl to a phenyl because bioisosteric replacements often lead to enhanced or similar biological activity, and phenyl and thienyl were well-known bioisosteres in the antifolate context. (Id. at ¶¶ 57-60.)

The court concludes that the ways in which a person of ordinary skill in the art would

modify the thienyl compound would not result in pemetrexed. The evidence presented at trial indicates that a person of ordinary skill in the art would change the amino at the 2-position of the thienyl compound to a methyl to improve the TS inhibitor, and would change the carbon-carbon bridge of the thienyl compound to a carbon-nitrogen bridge, or add an ethyl portion to the carbon-carbon bridge, which would not result in pemetrexed. (D.I. 109 at 534-49; 561-72.) Moreover, the evidence adduced at trial indicates that a person of ordinary skill in the art would not have reason to make changes to the aryl region of the thienyl compound because the TS art taught that the combination of 2-amino and phenyl in the aryl region was undesirable. (D.I. 111 at 984:15-18.) Even if enzyme targets such as DHFR or GARFT inhibitors were considered, the art taught away from making pemetrexed. (D.I. 109 at 567-68; 574-75.)

The court rejects the defendants' arguments regarding the bioisosterism[5] of thienyl and phenyl because bioisosterism gives no indication about whether the new compound will be better or worse than the previous compound, how well it will bind to the enzyme, or what the overall effect of the binding may be, meaning that the new compound may have opposite activity as compared to the previous compound. (D.I. 108 at 443-44; D.I. 111 at 993-94.) As a result, the court concludes that a person of ordinary skill in the art would not rely on bioisosterism to determine what modifications to make to the thienyl compound, and the defendants oversimplified the science by focusing only on the aryl region of the thienyl compound in isolation.

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[5]Bioisosterism stands for the principle that if certain modifications are made to a compound, the resulting compound will bind to the same enzyme as the starting compound. (D.I. 108 at 443-44; D.I. 111 at 993-94.)

IV. CONCLUSION

Based on the factual record in this case, the documentary and testimonial evidence presented at trial, the court concludes that the defendants have not proven the invalidity by obviousness-type double patenting of the '932 patent. An order shall issue entering judgment in favor of the plaintiffs.

Dated: July 28, 2011

CHIEF, UNITED STATES DISTRICT JUDGE

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ORDER

At Wilmington, this 27th day of July, 2011, consistent with the memorandum opinion issued this same date, IT IS HEREBY ORDERED that:

1. The '932 patent is not invalid for obviousness-type double patenting.

2. The Clerk of Court is directed to enter judgment in favor of the plaintiffs and against the defendants.

Dated: July 28, 2011

CHIEF, UNITED STATES DISTRICT JUDGE